estimate becomes more reliable. But it is optimal to *not use* the second source — or at least to weight it differently — if the system knows that there is a chance that the modality signals may be biased relative to one another, which might occur during body growth or tool use. In this case, there is a potential cost in using the second source of information because the combined estimate would be biased [16,18]. Adults seem to be able to use the available sensory information differently depending on the task demands and to adjust their perceptual estimates in order to minimize the cost or to maximize the benefit [19]. Perhaps children take longer to learn that.

In summary, the empirical evidence that optimal integration occurs relatively late in a child's development is strong. But why integration emerges so late and which stage in the integration process is suboptimal are still open questions.

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Phagocytic Signaling: You Can Touch, but You Can't Eat

The ability of phagocytes to discriminate between viable/healthy and apoptotic/foreign/abnormal cells is of fundamental importance; a recent study provides new molecular insights into the function of CD47–SIRPα signaling in this discrimination.

Jason M. Kinchen and Kodi S. Ravichandran

On a daily basis, the human body turns over 100–200 billion cells, including unwanted cells that do not have the right developmental fitness (for example, during hematopoiesis), superfluous cells (such as excess lymphocytes that remain after a pathogenic challenge has been removed), and damaged or aged cells (such as aged erythrocytes) that need to be removed as part of the cellular homeostasis in the body. The turnover of these cells begins with the induction of an apoptotic program or other cellular changes that mark them for removal, and continues with the subsequent recognition of altered features by phagocytes, leading to a highly efficient and immunologically silent removal of these unwanted/dying cells [1]. The phagocytes that carry out this clean-up exercise include macrophages, dendritic cells, Kupffer cells of the liver (e.g. for removal of aged erythrocytes) as well as many neighboring cells, although the relative contribution of each type of phagocyte is unknown. Inherent in this clean-up process is the need to specifically and selectively remove unwanted cells whilst sparing neighboring healthy cells that are found within the same tissue milieu.

The discrimination of the healthy from the unwanted/aged/dying cells appears to be achieved at two levels. First, the cells intended for removal display markers or ligands called 'eat-me' signals, i.e. 'altered self', which can in turn be recognized by receptors on the phagocytes. Second, healthy cells appear to have markers called 'don't-eat-me' signals that actively inhibit phagocytosis [1–4]; these signals are either downregulated in the dying cells or present in an altered conformation. While significant strides in recent years have been made towards our understanding of eat-me signals and their recognition (see [1,5], for review), progress in our understanding of how don't-eat-me signals function has been slower. The cell-surface protein CD47 on healthy cells and its engagement of a phagocyte receptor, SIRPα, appears to constitute a key don't-eat-me signal. A recent study [6] now sheds light on the molecular events that are negatively affected by CD47–SIRPα signaling with larger implications for our understanding of the phagocytic process (Figure 1).

Phagocytes use a broad variety of receptors to recognize the altered-self state. Typically, the steps in phagocytosis involve the recognition

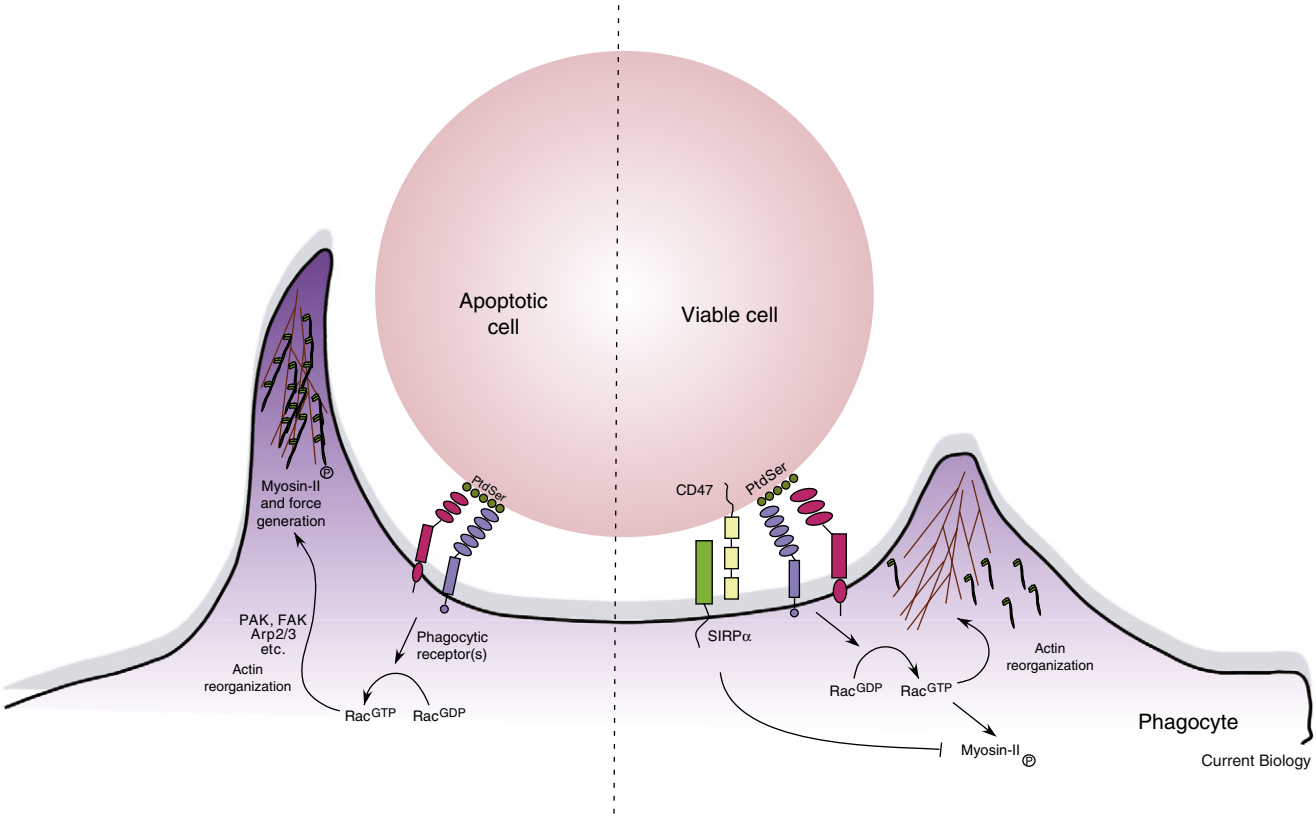

Figure 1. CD47–SIRPα signaling inhibits internalization of viable cells.

Recognition of apoptotic cells, either through exposed phosphatidylserine (PtdSer) or other opsonins, results in the activation of the Rac GTPase, extension of lamellipodia around the target, and ultimately internalization. CD47–SIRPα signaling, which inhibits the inappropriate internalization of viable cells, is downmodulated during apoptosis.

of one or more ligands on the cells marked for removal by specific receptors on the phagocytes with the formation of a 'phagocytic synapse', the generation of an actin-rich phagocytic cup at the phagocytic synapse, extension of the phagocytic arms around the target through cytoskeletal rearrangements, and, ultimately, the pulling of the target into the phagocyte through force generated by motor proteins (Figure 1). While don't-eat-me signals have been shown to prevent the inappropriate removal of living cells, how signaling negatively impacts particle internalization has not been fully elucidated. For example, inhibition of CD47-mediated engagement of SIRPα on the phagocyte or loss of CD47 expression in knockout mice can cause removal of live cells and non-aged erythrocytes [2,7]. Alternatively, blocking SIRPα recognition also allows engulfment of targets that are not normally engulfed.

How does SIRPα signaling block the active process of engulfment? On the basis of studies in other contexts, SIRPα can be tyrosine phosphorylated when crosslinked and can recruit, via its cytoplasmic tail, the tyrosine phosphatase SHP-1 [8]. This led to the hypothesis that CD47–SIRPα signaling may regulate the phosphorylation state of phagocytic receptors or effector proteins. However, features of this model have remained largely untested until recently.

A recent paper by Tsai and Discher [6] has addressed the molecular mechanism by which the CD47–SIRPα module negatively regulates phagocytosis. They use human monocyte cell lines or primary human monocytes with two broad types of target to further address the role played by CD47 and SIRPα. The first targets are sheep or human erythrocytes. Previous studies have shown that CD47-mediated recognition of SIRPα is species specific [9]: human SIRPα does not recognize CD47 expressed on sheep erythrocytes, resulting in a high level of basal uptake of the sheep erythrocytes by human macrophages, but little uptake of human erythrocytes. Adding soluble human CD47 along with the sheep erythrocytes inhibits uptake, demonstrating that human CD47–SIRPα engagement alone is sufficient to block internalization in this assay. The authors also elegantly use the purified human CD47 to obtain a quantitative estimate of the amount of phagocyte SIRPα engagement that is necessary for the inhibitory signal (10–20% of the normal CD47 density in erythrocytes is sufficient to inhibit phagocytosis). The second type of target that the authors use in their studies is a simplified one, where the uptake of immunoglobulin G (IgG)-opsonized beads is mediated via the activating Fc receptor (FcR) on human macrophages; coating these beads with varying amounts of purified human CD47 allows the simultaneous engagement of the FcR and SIRPα, in turn leading to inhibition of uptake. The authors then take advantage of these two target systems coupled with microscopy-based analyses to address the localization of various

signaling proteins involved in uptake and make several intriguing observations.

First, SIRPα ligation does not inhibit binding of phagocytic receptors to the target or receptor activation, but instead inhibits downstream signaling events. This is supported by observations that adhesion of opsonized erythrocytes and actin enrichment adjacent to the target are both unaffected by CD47–SIRPα engagement, as is phosphorylation of the scaffold protein paxillin (and its recruitment to the phagocytic cup). The authors then demonstrate that the motor protein non-muscle myosin IIa, which can provide the pulling forces for dragging the targets into the phagocyte, is enriched at the phagocytic cup during early stages of particle internalization (Figure 1). Surprisingly, myosin IIa recruitment is reduced and/or transient in the context of CD47–SIRPα signaling. Since the function of SIRPα depends on its binding to the tyrosine phosphatase SHP-1, the authors used a proteomic approach to look for proteins with decreased phosphorylation following SIRPα ligation. Among the three proteins they identify, the one most relevant for this discussion is myosin IIa. The authors further narrow this phosphorylation down to two evolutionarily conserved potential phosphorylation sites on the myosin head domain.

Phosphorylation has been shown to promote the assembly of myosin II on actin fibers [10]. Consistent with this notion, the decreased phosphorylation of myosin IIa achieved through engagement of SIRPα or expression of a tyrosine-phosphorylation-defective form of myosin IIa inhibits engulfment of sheep erythrocytes and opsonized beads. Moreover, siRNA-mediated knockdown of myosin IIa also decreased phagocytosis; actin was still enriched at the immune synapse, similar to what is seen when phagocytosis is blocked by CD47–SIRPα engagement. Taken together, this work identifies regulation of the phosphorylation status of myosin IIa as a potential point of regulation for CD47–SIRPα signaling.

How does this work enhance our overall knowledge of phagocytosis and cell clearance in the body? First, it demonstrates that CD47 engagement of SIRPα can serve as a generic don't-eat-me signal that can turn off engulfment mediated by multiple modalities, including apoptotic cell clearance (as has been demonstrated previously) and FcR-mediated phagocytosis. This is particularly interesting, since inhibitory Fc receptors (such as FcγRIIB) can also downmodulate activating types of FcR, although this is mediated through a lipid phosphatase and degradation of phosphoinositide (3,4,5) triphosphate [11]. In contrast to FcR-mediated uptake, apoptotic cell engulfment involves multiple ligands and a variety of classes of receptor, including tyrosine kinase receptors [12], lectins, integrins [13,14], Ig-domain proteins [15], and seven transmembrane receptors [16]. How a single CD47–SIRPα module could inhibit signals downstream of multiple different receptors was of some concern; however, the observation by Tsai and Discher [6] that the early steps of recognition and actin polymerization are largely unaffected by CD47–SIRPα signaling may provide a clue.

This work also indirectly suggests a key role for myosin IIa and non-muscle myosins in apoptotic cell clearance. To date, myosin IIa and its homologues have not been identified in the context of mammalian apoptotic cell engulfment or in model organisms, although other motor proteins (e.g. dynein) have been identified in unbiased screens [17]. How myosin IIa may be recruited and regulated by signals generated during recognition of apoptotic cells, and how the pulling forces are generated could be of considerable interest. Other negative signals have also been identified for the removal of apoptotic cells: GTP-bound RhoA may serve as a 'brake' to limit the engulfment of apoptotic cells, as downmodulation of RhoA activity can promote engulfment [18]. Similarly, CD31 has also been shown to promote the disengagement of live cells after they engage the phagocyte [4]. How CD47–SIRPα signaling may integrate with these other negative regulators remains to be seen, although one possibility is that coordinated signaling of these players is required for disassembly/resolution of the 'phagocytic synapse'. In this respect, it would be worthwhile to know whether CD47–SIRPα signaling is eventually overcome, or whether the phagocytic synapse will resolve itself over time.

Lastly, CD47-deficient mice show inappropriate removal of erythrocytes [7], leading to the development of autoimmune conditions in certain genetic backgrounds [19]. Similarly, failed clearance of apoptotic cells has also been shown to lead to autoimmune phenotypes. Whether the signals derived from the CD47–SIRPα module also somehow contribute to the anti-inflammatory signaling response of phagocytes during apoptotic cell engulfment remains to be determined. Non-professional phagocytes, which typically do not express CD31 or SIRPα (but do express CD47, reviewed in [3]), have been shown to play key roles in apoptotic cell removal *in vivo* [20]. At this time, it is unknown whether a protein with similar function to SIRPα (using CD47 as a self-ligand) or an entirely different system is employed to prevent inappropriate removal of cells by non-professional phagocytes.

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Social Cognition: Hi There! Here's Something Interesting

A new study of gaze following shows that human infants are highly sensitive to the communicative intent of the person they are interacting with.

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We do not always need direct experience to learn about the world. We can use the social information acquired by watching other creatures [1]. The circling of vultures indicates the location of a carcass, and the greatest crush of people at a reception indicates the location of the free drinks. Social information can also indicate the quality of resources. Rats faced with unfamiliar food use cues provided on the breath of their companions to decide what to eat [2], and, when walking though an unfamiliar town, we will avoid restaurants in which very few diners are sitting. Learning from social information is especially important for infants who have, as yet, little knowledge and little opportunity for independent exploration. An article published recently in *Current Biology* [3] suggests that, in contrast to other animals, human infants when they learn from observation are highly sensitive to the communicative intent of their teacher.

Eye-gaze direction is an important source of social information, especially for humans. We are exquisitely sensitive to eye-gaze direction [4], partly because the human eye has a widely exposed white sclera surrounding the darker coloured iris [5]. Furthermore, when we see someone move their eyes we seem to have a strong wish to know what they are looking at. By following other people's eye gaze we can discover what they are interested in and acquire clues about their wishes and intentions [6]. Attention to the direction of eye gaze appears to be obligatory. If we see a face with eyes looking to the right, we will automatically attend to the right side of the visual field. This is indicated by faster reaction times to targets appearing subsequently in the same visual field. This cuing effect occurs even when the cues to the position of the target are consistently invalid [7].

Our automatic response of making a shift of attention when we see someone else move their eyes is part of a more general phenomenon whereby observing the behaviour of others elicits corresponding motor responses in the observer. Thus, eye movements are part of the 'mirror neuron' system [8]. The possible role of this system in reading minds and enabling the evolution of language has been much exaggerated [9]; however, it has a very important function in allowing us to use our own motor system to emulate the behaviour of others. Through such emulation we can generate predictions about the unfolding actions of the person we are observing [10,11].

Nevertheless, there is a problem for the mirror system. There are many situations in which automatic imitation of the behaviour of others is not desirable. For example, during joint action we frequently need to make movements that are different from the person we are cooperating with. When carrying a table together, one person may walk forwards while the other walks backwards [12]. Even for a simple joint action like gaze following, direct mirroring may not be appropriate. To look at what you are looking at may require me to make a very different movement with my eyes. Furthermore, there is the problem of what happens when we are in a group; who do we imitate? One study [13] suggests a possible answer to these questions. In this experiment, participants observed someone moving their left or their right arm. When the actor was facing the observer, significant mirror activity was elicited in the observer's brain. When the actor had her back to the observer, however, this was not the case — her movements did not elicit any mirror activity. The authors speculate that actions have more social relevance when the actor is facing the observer, and that this social relevance acts as a gatekeeper for the mirror system.

The idea that we only emulate actions that have social relevance points to an important distinction within social information. So far I have talked largely about inadvertent social information (termed social cues in [1]). However, in humans in particular, there is the much more important class of social information that is deliberately communicative (social signals). Directed speech is the most obvious example of a human social signal, but any action can be deliberately communicative including eye movements.